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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/644,289	05/10/1996	MOLLY F. KULESZ-MARTIN	RPP:135D-US	4031

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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31

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/644,289	KULESZ-MARTIN, MOLLY F.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-19* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-11 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 3-6, 8-11, 15-19 are being examined.

The following are the remaining rejections.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

The amended claim 1 now contains a polynucleotide sequence which is not accompanied by a sequence identification number.

REJECTION UNDER 35 USC FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

Claims 1, 3-4, 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 3-4, 17 are drawn to a plasmid containing a cDNA sequence which encodes a protein designated p53as. Said p53as is sequentially the same as wild type

p53 up to the final 50 carboxy terminal amino acids of p53. Said p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus. Said negative regulatory domain must be activated in p53 or p53 to have active DNA binding. Said p53as and activated p53 bind to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" . Said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53.

The specification does not disclose that p53as and activated p53 bind to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT".

REJECTION UNDER 35 USC FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claims 15-16 are drawn to a plasmid containing a p53as gene sequence encoding the peptide of SEQ ID NO:1 or a portion of the peptide of SEQ ID NO:1, which peptide will raise an antibody response. Claim 19 is drawn to a viral vector containing a

p53as gene sequence encoding the peptide of SEQ ID NO:1 or a portion of the peptide of SEQ ID NO:1, which peptide will raise an antibody response.

It is noted that a p53as gene sequence encoding the peptide of SEQ ID NO:1 or a portion of the peptide of SEQ ID NO:1 encompass a sequence of any length and any structure provide it comprises a fragment of the full length p53as gene sequence, wherein said fragment encodes the peptide of SEQ ID NO:1 or a portion of the peptide of SEQ ID NO:1. It is further noted that a portion could be as little as a few amino acids. In addition, it is noted that a p53as gene sequence encompass a genomic p53as sequence.

The specification discloses a p53as cDNA sequence, which is a splice variant of the wild type p53.

The claims, as written, however, encompass polynucleotides which vary substantially in length and also in nucleotide composition. The broadly claimed genus additionally, encompasses p53as gene sequence, as well as genes incorporating only portions of the disclosed sequence.

The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d

1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural freatures that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

The specification further fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined (Harris et al. J. of The Am Society of Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and skilled in the art would therefore not recognize from the disclosure that applicant was in possession of the genus of nucleic acid, including genes, comprising SEQ ID NO: X or fragments thereof.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Thus, only a p53as polynucleotide sequence which consists of a polynucleotide sequence encoding a polypeptide sequence consisting of the peptide of SEQ ID NO:1, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 102

withdrawn Rejection under 35 USC 102 of claim 16 pertaining to anticipation by Arai et al remains for reasons already of record in paper No.29.

Applicant submits a Declaration by Dr. Molly Kulesz-Martin, asserting that the p53-M8 disclosed by Arai et al is different from the claimed p53as, since they do not have the same sequence or function. Applicant further asserts that there is no suggestion in Arai et al that any particular portion of p53-M8 should be encoded into a plasmid which portion is all or part of the sequence specifically set forth in claim 16. Further, a portion of the sequence set forth in claim 16 will raise an antibody response, such result is not suggested by nor obvious by any disclosure of Arai et al.

Applicant asserts that it is generally believed that a peptide sequence must be at least 8 or 9 amino acid in length, before an antibody response is possible. Any sequence of 8 or ten or more amino acids of the claimed SEQ ID NO:1 could be tested for antibody response and could be used to distinguish p53 from p53as.

The submission of the Declaration by Dr. Molly Kulesz-Martin is acknowledged.

Applicant's arguments set forth in paper No.30 have been considered but are not deemed to be persuasive for the following reasons:

The plasmid containing the sequence taught by Arai et al meets all the limitation of the claim. It is noted that a portion of SEQ ID NO:1 could be a few amino acids. Thus sequence taught by Arai et al clearly encodes a portion of SEQ ID NO:1. Further, the claim does not have the limitation that the portion of SEQ ID NO:1 raises an antibody response. The claim only has the limitation that the peptide of SEQ ID NO;1 raise an antibody response, which is an inherent property of SEQ ID NO:1.

The reference does not specifically teach that the alternative spliced p53 encodes a portion of the peptide of SEQ ID NO:1, which peptide will raise an antibody response. However, the claimed plasmid containing a p53as gene sequence appears to be the same as the prior art plasmid containing an alternative spliced p53 sequence. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable

diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

REJECTION UNDER 35 USC 103, NEW REJECTION

Claims 1, 3-4, 17 are rejected under 35 USC 103 as being obvious over Han et al (of record), in view of Sambrook et al (of record), Hupp et al, 1992, Cell, 71: 875-886, and Funk, WD et al, 1992, Mol Cell Biol, 12: 2866-2871.

Claims 1, 3-4, 17 are amended to be drawn to a plasmid containing a cDNA sequence which encodes a protein designated p53as. Said p53as is sequentially the same as wild type p53 up to the final 50 carboxy terminal amino acids of p53. Said p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus. Said negative regulatory domain must be activated in p53 for p53 to have active DNA binding. Said p53as and activated p53 bind to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" . Said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53.

The teaching of Han et al and Sambrook et al has been set forth.

Han et al teach making of cDNAs from alternatively spliced p53 RNA in transformed and normal murine epidermal cells, using reverse transcriptase. Han et al further teach using polymerase chain reaction, and specific primers to amplify fragments

from said cDNA, which are cloned into plasmids for sequencing. Han et al also teach that sequence analysis of the plasmids show regions representing regularly spliced wild type p53, and alternative splicing at the 3' end of intron 10. The alternatively spliced species AS-p53 are predicted to result in premature termination of p53 protein, making it 9 amino acid shorter and differing in 25 amino acids at the C-terminus. Otherwise, the molecule is identical to wild type p53 (See the abstract, p.1980, column 2, last paragraph to p.1981, column 1, first paragraph and third paragraph). Han et al further teach that the carboxy terminus of the protein translated from AS-p53 is predicted to be quite distinct from the wild type R-p53 by having reduced basic charges, which could influence the secondary structure of p53 (p. 1981, first column, last paragraph). In addition Han et al teach that the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes and that more precise biochemical and **biological characterization** (emphasis added) of AS-p53 protein along with R-p53 protein appear to be critical in **future studies of p53 function** (emphasis added) in normal cells and in oncogenesis. (p. 1981, first column, last paragraph bridging second column, first paragraph).

Han et al do not teach a plasmid containing full length p53as cDNA, and a cell transformed with said plasmid. Han et al do not teach that p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus. Han et al do not teach that said negative regulatory domain must be activated in p53 for p53 to have active DNA binding, and that said

p53as and activated p53 bind to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" . Han et al do not teach that said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53.

Sambrook et al teach that expressing large amounts of proteins from cloned genes in plasmids is an art standard technique, and is valuable to the purification, localization, and functional analysis of the proteins. Sambrook et al also teach intact native proteins have been produced in large amount in *E. Coli* for functional studies (p. 17.2, lines 10-11). Thus a host cell, i.e. E. Coli, transfected with a plasmid for expressing intact proteins is taught by Sambrook et al.

Hupp et al teach that it is the C-terminus that inhibits DNA binding of wild type p53, and that removal of the 30 C-terminal amino acids constitutively activates p53, suggesting that this region plays a regulatory role in controlling p53 activity (p.876, first column, first paragraph, p. 878, second column, last parargraph). Hupp et al teach that altering the conformation of the C-terminal amino acid motif or removal of the C-terminal domain or binding of a monoclonal antibody specific for C-terminus of p53 would activate p53 DNA binding (p. 881, first column, second paragraph). Hupp et al also teach a consensus DNA binding site for p53.

Funk et al teach a DNA binding site for human p53.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to clone a full length p53as cDNA into plasmid for the following reasons: 1) To study function of a protein, i.e. p53 and AS-p53, as suggested

by Han et al, and Sambrook et al, it is art standard to incorporate a full length polynucleotide sequence into a plasmid to express and obtain a full length or intact native protein, as taught by Sambrook et al, because it is well known in the art that fragments of a protein usually would not have biological activity, as evidenced by Sambrook et al, who also teach that for functional study, large amount of **intact native protein** (emphasis added) are produced. Furthermore, the full length p53as protein could be readily obtained by routine techniques of cloning and expressing a plasmid containing a full length cDNA, for producing intact native protein, as taught by Sambrook et al, 2) The existence of a full length p53as cDNA is known from the teaching of Han et al, because Han et al teach its predicted protein, as being prematurely terminated as compared to p53 protein, and having 9 amino acid shorter and differing in 25 amino acids at the C-terminus, as compared to p53 protein. Furthermore, although Han et al do not directly teach the structure of a full length p53as cDNA, one of ordinary skill in the art could readily obtained it, in view of the available information concerning the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA, as taught by Han et al. The alternative spliced RNA of p53 taught by Han et al seems to be same the claimed p53as sequence, i.e., being different from the wild type p53 within the final 50 carboxy-terminal amino acids so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, wherein said negative regulatory domain must be activated in p53 or p53 to have active DNA binding, because, as evidenced by Hupp et al, it is the C-terminus that inhibits

DNA binding of wild type p53, and removal of the 30 C-terminal amino acids or change in the conformation of the C-terminus would activate p53 DNA binding, suggesting that this region plays a regulatory role in controlling p53 activity. Further, in view of the teaching by Hupp et al and Han et al, one would have expected that the AS-p53 taught by Han et al would have a different conformation at the C-terminus, and thus would be activated to bind to DNA, wherein the DNA binding sequence is the same as the sequence "AGGCATGCCT/ AGGCATGCCT", bound by activated wild type 53, as taught by Funk et al. In addition, one would have expected that the 25 C-terminal amino acids of the AS-p53 protein taught by Han et al would elicit an antibody which is specific for AS-p53 but not with p53, because said 25 C-terminal amino acids are different from the C-terminal amino acids of the wild type p53, as taught by Han et al.

The reference does not specifically teach that p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, wherein said negative regulatory domain must be activated in p53 for p53 to have active DNA binding, said p53as and activated p53 binding to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" , and aid p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53. However, the claimed cDNA sequence encoding p53as appears to be the same as the prior art cDNA sequence encoding AS-p53, absent a showing of unobvious differences. The office does not have the facilities and resources to provide

the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

The motivation is obvious, i.e. to obtain full length protein expressed by plasmid containing full length p53as cDNA for studying the function of p53as, since the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes and it is critical to include p53as in the study of the function of p53, as suggested by Han et al.

ANSWERS TO APPLICANT'S ARGUMENTS AGAINST THE REJECTION UNDER 35 USC 103 FOR CLAIMS 1, 3-4, 17

Applicant argues that Han et al is interested in sequencing not function when considering incorporating portions of a DNA sequence encoding a p53 type protein and that the Examiner has taken a quantum hindsight leap by concluding that Han et al is somehow interested in function in conjunction with incorporating such fragments into a plasmid. Applicant asserts that based on hindsight, the Examiner combines Sambrook et al, having no suggestion at al related to p53 sequences, or sequencing or function, and somehow concludes that one should incorporate the entire p53as sequence into a

plasmid, which is directly contrary to the specific teaching of Han et al, for the purpose for determining function, which is again contrary to the purposes of Han et al.

Applicant asserts that according to the Examiner reasoning, incorporating any novel sequence into plasmid would thus now be unpatentable no matter what the reason for incorporation.

Applicant's arguments set forth in paper No.30 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that it is a misinterpretation by Applicant of the Examiner position when Applicant asserts that the Examiner concludes that Han et al is somehow interested in function in conjunction with incorporating such p53 type fragments into a plasmid. The Examiner did not conclude that Han et al is interested in function "in conjunction" with incorporating such p53 type fragments into a plasmid.

The Examiner stated that besides teaching sequencing of a fragment of an alternative spliced p53, AS-p53, Han et al further teach that "more precise biochemical and biological characterization of AS-p53 appear to be critical in future studies of p53 function in normal cells and in oncogenesis (p.1981, column 2, first paragraph). In other word, although Han et al do not directly suggest incorporation of full length p53as into plasmid, the teaching of incorporation of full length sequence into plasmid is disclosed by Sambrook et al. Han et al provide motivation for cloning and sequencing full length AS-p53. That is the motivation is to determine precise biochemical and biological characterization of AS-p53, which would be critical in future studies of p53 function in normal cells and in oncogenesis, since the differences in the carboxy terminus between

AS-p53 and R-53 protein could lead to significant biochemical and biological changes, in view of the teaching of Sambrook et al that expressing large amounts of proteins from cloned genes in plasmids is an art standard technique, and is valuable to the purification, localization, and functional analysis of the proteins, and that "intact" native proteins have been produced in large amount in *E. Coli* for functional studies (p. 17.2, lines 10-11).

Thus contrary to Applicant assertion, incorporating the entire p53as sequence into a plasmid is not contrary to the specific teaching of Han et al, but is suggested by the teaching of Sambrook et al of incorporating the full length sequences into plasmids for making intact native proteins, for the purpose of functional analysis of proteins, which is also suggested by Han et al for the specific p53as protein, and is not contrary to the purposes of Han et al.

Moreover, it is a misinterpretation by Applicant when Applicant asserts that the Examiner reasoned that incorporating any novel sequence into plasmid would now be unpatentable no matter what the reason for incorporation.

The Examiner stated that incorporation of a sequence which is known in the art into a plasmid, i.e. the full length p53as taught by Han et al, would be obvious. Han et al discloses cloning and sequencing of a fragment of an alternative spliced species of p53, AS p53, wherein said alternative splicing is predicted to result in premature termination of p53 protein, making it 9 amino acid shorter, and differing in 25 amino acids at the C-terminus. Otherwise the molecule is the same as the wild type p53 (Han et al, abstract, page 1980, column 2, last paragraph, bridging page 1981, column 1, first paragraph and

third paragraph). Thus the alternative spliced RNA of p53 taught by Han et al seems to be same the claimed p53as sequence, being different from the wild type p53 within the final 50 carboxy-terminal amino acids so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, *supra*. Further, the existence of full length p53as cDNA is known from the teaching of Han et al, because Han et al teach its predicted protein, as being prematurely terminated as compared to wild type p53, making it 9 amino acid shorter, and differing in 25 amino acids at the C-terminus. Furthermore, although Han et al do not directly teach the structure of a full length p53as cDNA, one of ordinary skill in the art could readily obtain it, in view of the available information concerning the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA, as taught by Han et al (Han et al, page 1979,second column, last paragraph, bridging page 1980, first column, first paragraph). Thus it would be obvious to incorporate the full length p53as sequence into a plasmid , wherein the full length p53as sequence could be obtained from the teaching of Han et al, for the purpose of analysis of function of p53as, as taught by Han et al and Sambrook et al.

REJECTION UNDER 35 USC 103

1. Claims 5-6, 8-11 and 18 remain rejected under 35 USC 103 as being obvious over Han et al in view of Lee et al for reasons already of record in paper No.29.

Applicant argues that the Examiner argues that Han et al suggests incorporation of p53as into plasmid for the purpose of studying function. Applicant argues that Han et

al does no such thing, and that Han incorporates nothing at all into viruses for any purpose. Applicant argues that except based upon hindsight, there is no reason at all to combine Han et al with Lee et al. Applicant argues that Lee et al is concerned with viral vectors, but suggest nothing concerning p53 sequence for any purpose and recognizes no purpose for incorporation of a p53 type sequence into a virus. Applicant asked what would be the function or purpose for such incorporation be?

Applicant's arguments set forth in paper No.30 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that it is a misinterpretation by Applicant when Applicant asserts that the Examiner position is that Han et al suggests incorporation of p53as into plasmid for the purpose of studying function.

The Examiner stated that besides teaching sequencing of a fragment of an alternative spliced p53, AS-p53, Han et al further teach that "more precise biochemical and biological characterization of AS-p53 appear to be critical in future studies of p53 function in normal cells and in oncogenesis (p.1981, column 2, first paragraph). In other word, although Han et al do not directly suggest incorporation of full length p53as into viral vectors, the teaching of incorporation of full length sequence into viral vectors is disclosed by Lee et al. Han et al provide motivation for cloning and sequencing full length AS-p53. That is the motivation is to determine precise biochemical and biological characterization of AS-p53, which would be critical in future studies of p53 function in normal cells and in oncogenesis, since the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes,

in view of the teaching of Lee et al of the importance and advantages of using viral vector to obtain intact, biochemically active protein in large quantities to advance investigation of the properties of that protein.

Thus it would have been obvious to incorporate a known sequence into a viral vector, i.e. the full length AS-p53 sequence that one could obtain from the teaching of Han et al. The purpose of said incorporation into a viral vector is to produce intact protein to study its function, as taught by Lee et al and Han et al.

2. Claim 19 remains rejected under 35 USC 103 as being obvious over Arai et al in view of Lee et al and Sambrook et al for reasons already of record in paper No.29.

Applicant argues that Arai et al sequence and function is different from the presently claimed sequences and function, and that Arai et al do not discloses the presently claimed sequence alone or within any vector. Applicant further argues that Lee suggest nothing concerning any sequence remotely related to the claimed sequence.

Applicant's arguments set forth in paper No.30 have been considered but are not deemed to be persuasive for the following reasons:

- The sequence taught by Arai et al meets all the limitation of the claim, and seems to be the same as the claimed a sequence encoding a portion of SEQ ID NO:1, *supra*.

Moreover, it would have been obvious to incorporate the sequence taught by Arai et al into a viral vector as taught by Lee et al, for the purpose of studying function of the encoded protein, as taught by Lee et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

February 27, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER